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197 14-3-3 ϵ and 14-3-3 σ proteins link inflammatory pathways to Cancer progression and prevention

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Inflammation has long been associated with the development of cancer. However, the exact reflexive relationship between the two has not been elucidated well. With the aim of linking inflammatory pathways to carcinogenesis, our group are exploring the role of oncoviruses and novel immunological molecules in carcinogenesis. To this end, we have functionally characterized a group of 14-3-3 proteins which has been implicated to play a regulatory role in cancer development. We show that 14-3-3 ϵ and 14-3-3 σ play a major regulatory role in signalling through Toll-like receptors (TLR), which represents the first line of defense in humans upon microbial infections. We have shown that both of these proteins impair TLR3 and TLR4 ligand-induced IL-6, TNF α and IFN- β production. We have also shown that 14-3-3 ϵ and 14-3-3 σ impairs TLR3 and TLR4 mediated NF- κ B and IFN- β reporter gene activity. Interestingly, whilst the 14-3-3 proteins inhibit TLR3 mediated CCL5 mRNA and protein production, 14-3-3 proteins augment TLR4-mediated production of CCL5 in a Mal/MyD88-dependent manner. 14-3-3 ϵ and 14-3-3 σ also bind to the TLR adaptors proteins and to both TRAF3 and TRAF6. Given that our study conclusively shows that 14-3-3 ϵ and 14-3-3 σ play a major regulatory role in balancing the host inflammatory response to viral and bacterial infections through modulation of the TLR signalling pathway, manipulation of 14-3-3 proteins may represent novel therapeutic targets for inflammatory conditions and cancer progression and prevention.

References:

Aisha Qasim Butt and Sinead M. Miggin (2012) Cancer & Viruses: A Double-Edged Sword. Accepted for publication. *Proteomics. In Press.*
Aisha Qasim Butt, Suaad Ahmed, Ashwini Maratha and Sinéad M. Miggin (2012) 14-3-3 ϵ and 14-3-3 σ inhibit TLR3 and TLR4 mediated pro-inflammatory cytokine induction. *Submitted to J Biol Chem.*
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198 Increased subcutaneous B16 melanoma cell-derived primary tumor growth in STAT6 deficient mice

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Tumor tissue contains different immune cells which can generate an immune response against tumor cells. Paradoxically, the developing tumor can often induce a pro-tumoral immune-microenvironment which inhibits anti-tumor immunity while enhancing tumor growth, invasion and vascularization. Th2 cells and M2 macrophages inhibit anti-tumor immunity as well as promote tissue remodelling and tumor progression. However, some in vitro results suggest that M2 macrophages can also inhibit tumor cell proliferation. STAT6 transcription factor has a central role in the development of Th2 cells and M2 macrophages, since it transmits the signal of Th2 type cytokines (IL-4, IL-13) towards the nucleus controlling the expression of hundreds of target genes. Th2 type cytokines can be produced by tumor-infiltrating immune cells and, in some cases, also by tumor cells. In the absence of STAT6 an increased Th1 response, CD8 $^{+}$ cytotoxic T cell and M1 macrophage differentiation can be observed.

The main goal of our work was to determine the role of STAT6 transcription factor in tumor development using subcutaneous B16 mouse melanoma tumor model in STAT6 knock-out and wild type mice. Primary tumors were removed 14 days after inoculation and individual tumor weights were measured. We also examined the basal structure and macrophage content of tumors using immunohistochemistry, and characterized the tumor's immunological status with measurement of different immune cell markers by quantitative PCR.

Our results show an increased primary tumor growth in STAT6 deficient mice compared to the wild type animals. Basal structure of the tumor tissue was similar in both groups, but peripheral tumor cell infiltration to the neighboring tissues was enhanced in STAT6 deficient mice. Gene expression analysis of the tumor tissue revealed significant down-regulation of M2 macrophage marker arginase 1 and anti-inflammatory cytokine IL-10 in STAT6 knock-out mice-derived tumors. These results suggest that STAT6 may have an influence on primary tumor growth and have a role in controlling the phenotypic switch of tumor-infiltrating immune cells.